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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,247	BAR-OR, DAVID	
	Examiner	Art Unit	
	SAMUEL W. LIU	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46,49-53,81,186,194-199,217-220,246,272,273 and 280-299* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *272 and 273* is/are allowed.

6)☒ Claim(s) *46,49-53,81,186,194-199,217-220,246,280 and 282-299* is/are rejected.

7)☒ Claim(s) *281* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

------DETAILED ACTION

Status of the claims

Claims 46, 49-53, 81, 186, 194-199, 217-220, 246, 272-273, and 280-299 are pending.

The amendment filed 10/3/08 which amends claim 272 has been entered. Claims 1-45, 47-48, 54-80, 82-185, 187-193, 200-216, 221-245, 247-271 and 273-279 were cancelled by the amendment filed 11/20/06. Claims 46, 49-53, 81, 186, 194-199, 217-220, 246, 272-273, and 280-299 are thus examined in this Office action.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[1] Claims 46, 49-51, 81, 186, 194-197, 219-220, 246, 280, 282-284, 289-291, 295, and 297-299 remain, and claims 52-53, 198-199, 217, 285-286, 292-293 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wuelknitz et al. (US Pat. No. 5279814) in view of Jiang et al. (*J. Agric. Food Chem.* (2000) 48, 990-994) and Reynolds E. C. (US Pat. No. 6780844 B1).

Examiner remark;

The 103 rejection herein is due to the claim language "at least…dephosphorylated" which reads on **100%** dephosphorylated.

In patent claims 1-2, Wuelknitz et al. teach a dental composition comprising phosvitin wherein said dental composition is in form of a toothpaste or a gel (patent claim 2) or tooth cream or powder (col. 1, line 57), which is non-aqueous solution, and wherein "toothpaste" can be a toothpaste foam and the "gel" is an obvious variation of "cream", as applied to claims 46, 186, 219-220, 246, and 297-299.

Since claim 295 recitation "for topical administration to the skin of an animal" is considered to be an intended use for the pharmaceutical composition which has little patentable weight, claim 295 is included in the rejection.

The phosvitin is obtained from SIGMA (see col. 5, line 47) which is prepared from chicken egg yolk (see "*Discussion of art*" in the Office action mailed 5/23/07), as applied to claims 49 and 194.

Yet, Wuelknitz et al. do not expressly teach or suggest that the phosvitin or fragment thereof is at least 10%, or 35% or 50% dephosphorylated.

Jiang et al. teach that ability of phosvitin phosphopeptide ("PPP", see abstract) of solubilizing calcium from phosphate precipitate did nit increase with increase phosphoric groups in the "PPP" fragment (p.993, right col., lines 13-16), and teach that the tryptic "PPP" fragment has ability of inhibiting formation of insoluble calcium phosphate; for example, 65% dephosphorylation (i.e., 35% phosphate retention) shows the highest solubilization ability for the insoluble calcium phosphates (p. 993, left col., last paragraph, and p.994, left col., lines 10-12; Fig. 5). Also, Jiang et al. teach that "PPP" can be useful for a nutraceutical (p. 994, left column, last sentence) wherein the "nutraceutical" composition includes toothpaste.

Reynolds teaches that in the absence of the phosphopeptides, e.g., phosvitin (see col. 9, line 37), amorphous calcium phosphate (ACP) precipitates out of solution and transforms into insoluble crystalline hydroxyapatite (col. 2, lines 26-29); this precipitate (insoluble form) decreases calcium bioavailability and limits/inhibits anticariogenic activity (col. 2, lines 33-35). By contrast, ACP stabilized/solubilized by the phosphopeptides can be localized at the tooth surface to provide superior bioavailability, i.e., anticaries efficacy (col. 2, lines 44-49).

Further, Reynolds teaches that phosphopeptide-stabilization of ACP has benefit of increasing calcium bioavailability and preventing formation of dental caries, wherein said "stabilizing" take effect through phosphopeptide binding to ACP cluster to produce metastable solution in which nucleation growth of ACP crystal and precipitation is prevented (see abstract and col. 3, lines 41-47) and wherein said "stabilizing" refers to stabilized by the phosphopeptide and the stabilized form is the most soluble (see col. 2, lines 14"17), and thereby, the "stabilized" form is useful for toothpaste formulation (col. 3, lines 55-57), wherein the highly "stabilized" ACP is most soluble (col. 2, lines 16-17).

These suggest that increased bioavailability of calcium phosphate via forming soluble complex (i.e., "stabilizing" discussed above) with the phosphopeptide such as tryptic phosvitin phosphopeptide (PPP) in order to prevent precipitation of calcium phosphate is critical for ACP to be localized at the tooth surface so as to provide superior anticaries efficacy for the toothpaste formulation. These teachings establish a nexus between the dephosphorylation (e.g., 65%)-mediated solubilization of calcium-phosphate taught by Wuelknitz et al. and the ACP bioavailability determined anticaries property (through "stabilizing" phosphopeptide-CAP

complex) useful in formulating dental composition, e.g., toothpaste as taught by Reynolds, as applied to claim 46 and 186, and claims 50-51, 195-197, 280, 282-284 and 289-291.

Additionally, Jiang et al. suggests that an optimal requirement of phosphorylated group and different size of the phosvitin fragments (p. 993, right col., 2nd line for the bottom to p.994, left col., line 1), as applied to different % of dephosphorylation such as 70% and 90% (instant claims 52-53, 198-199, 285-286, 292-293).

Claim 217 limitation "formulated for topical administration" is considered to be an intended use which has little patentable weight because it does not appear to materially change the composition; and thus, claim 217 is included in the rejection. Alternatively, toothpaste is applied topically to the teeth and is not intended for ingestion.

Claim 81 is directed to a "kit" comprising instruction of using the kit, wherein said instruction is considered to have no patentable weight given by its own, and comprising a container holding the composition; wherein the "container" is obvious to any skilled artisan, and wherein the instruction and container will not alter the structure of the claimed pharmaceutical composition. See *In re Haller,* 73 USPQ 403 (CCPA 1946). Therefore, claim 81 is rejected.

It would have been obvious to one ordinary skill in the art at the time the invention was made to prepare the dental composition such as toothpastes, tooth powders, tooth gels, or tooth creams according to Wuelknitz et al. teaching, wherein said composition comprises the phosvitin fragment with about 65% dephosphorylated. This is because the 65% dephosphorylated (equal to 35% phosphate retained) phosvitin fragment has the highest solubility for the calcium phosphate precipitate due to its capability of inhibiting calcium phosphate precipitation, i.e., inhibiting formation insoluble calcium phosphate (see Figure 5, and p.993, section "*Formation of soluble*

complex with calcium", Jiang et al.) compared to 35% (65% phosphate retention), 82.5% (17.5% phosphate retention) dephosphorylation. And, this is because Reynolds has taught a correlation between the solubilization of the calcium phosphate precipitates and the "stabilized" form, i.e., the "phosphopeptides-calcium-phosphate bound complex" (soluble in solution) which, in turn, increases the bioavailability - allowing amorphous calcium phosphate (ACP) to be localized at the tooth surface to provide superior anticaries efficacy which benefits dentifrices such as toothpaste, as taught by Reynolds (col. 3, lines 55-58 and abstract).

This is also has been suggested by Jiang et al. who teach that the phosvitin fragment of 65% dephosphorylated which has the greatest ability of solubilizing calcium CPP [i.e., casein phosphopeptide] (see p. 990, line 11, Jiang et al.) can be useful as nutraceuticals which include dentifrices for toothpaste formulation.

In view of the attractive benefits discussed above and teachings regarding the extent of dephosphorylation directed solubilization/stabilization of the calcium phosphate by the phosphopeptides, e.g., "PPP", one skilled in the art would have readily formulated phosvitin fragment with ~ 65% dephosphorylated into dental composition, e.g., toothpaste, in order to enhance the bioavailability and anticaries efficacy of ACP in said composition with reasonable expectation of success. The percent or extent of said dephosphorylation" such as "35%", 50%," "70%" and "90%" which depends on size of partially hydrolyzed phosvitin fragments (*this "size"-dependent" issue has bee addressed in Jiang et al., from p. 993, right col., last two lines to p.994, line 1*) would have been within purview of ordinary skill and common sense of the artisan, and it would have been obvious for one skilled in the art to try it out, i.e., to extend the "65% dephosphorylation" to "35%", 50%," "70%" and "90" dephosphorylation of the "PPP"

fragment with different sizes thereof with reasonable expectation of success as well. Therefore, the combined reference teachings render the claims prima facie obvious.

[2] Claims 218 and 296 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wuelknitz et al. (US Pat. No. 5279814) in view of Jiang et al. (*J. Agric. Food Chem.* (2000) 48, 990-994) as applied to claims 186 and 194, and further in view of Shuch et al. (US Pat. No. 6503483).

The rejection of claims 186 and 194 are above.

Yet, neither Wuelknitz et al. nor Jiang et al. expressly teaches that the formulated composition is in drop form.

Shuch et al. teach that oral delivery system, i.e., formulation can be candy-gum "drops" (see col. 8, line62 to col. 9, line 2) (claim 218 and 296).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate said composition as drops because "drops" refer to small quantity of the formulation of claims 218 or/and 296. Within purview of ordinary skill and common sense, one skilled in the art would have chosen suitable formulation for a particular administration purpose, e.g., "drops" formulation for oral administration, as taught by Shuch et al. The nexus between the "drops" form and the "dental composition" is that both Shuch et al. and Wuelknitz et al. (col. 1, lines 55-58) teach the dental composition, wherein the "drops" suitable for topical application (col. 9, lines 4-5, Shuch e al.). Therefore, the combined reference teachings render the claims *prima facie* obvious.

The applicants' response to the 103 rejections

The response filed 10/3/08 submits that although Jiang et al. teach that dephosphorylated phosvitin fragment can be used to solubilized calcium, remove calcium from insoluble phosphate precipitates and inhibits formation of insoluble calcium phosphate; this teaching is inconsistent with the protection against demineralization by phosphoproteins discussed in Wuelknitz et al. reference (see p.11, last paragraph to p.12, 1st paragraph). The response asserts that inhibition of forming insoluble calcium phosphate is detrimental to tooth enamel (p.12, lines 1-3). Hence, the response infers that the skilled artisan would not be motivated by the references' teachings to use the dephosphorylated phosvitin peptide taught by Jiang in the dental composition of Wuelknitz et al., and thus, the requests withdrawal of the rejection.

The applicants' arguments are found unpersuasive because the references teach the dephosphorylated phosvitin phosphopeptide "PPP" has increased solubility of complex "PPP"-"ACP" [amorphous calcium phosphate] which is proportional to the increased bioavailability (col. 2, lines 14-31, Reynolds) which allow the ions such calcium and fluoride bound by the phosphopeptides to be able to be **co-localised** at the **tooth surface** (col. 3, lines 48-54, Reynolds); this prevents demineralization (col. 3,lines 42-47, Reynolds) s well as enables growth of hydroxyapatite (HA) crystal along the c-axis in enamel (col. 11, lines 41-47, Reynolds), suggesting that the dephosphorylated phosphopeptides such as "PPP" has positive effect on and/or protects enamel rather than the detrimental to tooth enamel asserted by applicants. In addition to this, the dephosphorylated "PPP" has property of enhancing said "bioavailability" and anticaries as taught by the combined teachings of Wuelknitz et al., Jiang et al. and Reynolds (see above.). Therefore, the 103 rejection is proper and stands.

It is of note that applicants' election filed 4/27/06 of Group 3 without traverse in response to the restriction requirement mailed 3/27/06.

Conclusion

Claims 272-273 are allowed. Claim 281 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Discussion of the art

The prior art made of record and not currently relied upon in any rejections is considered pertinent to Applicants' disclosure:

BNET business network (Nutraceutical Toothpaste Debuts (2008, updated) http://findarticles.com/p/articles/mi_hb4250/is_/ai_n13189892, pages 1-4) teaches that toothpaste is a nutraceutical composition.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

/Samuel W Liu/

Examiner, Art Unit 1656

December 15, 2008

/JON P WEBER/

Supervisory Patent Examiner, Art Unit 1657